=> d ibib abs hitstr l5 1-9

L5 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:238414 HCAPLUS
DOCUMENT NUMBER: 135:24537
TITLE: Novel peptide **conjugates** for tumor-specific chemotherapy
AUTHOR(S): Langer, Michael; **Kratz, Felix;** Rothen-Rutishauser, Barbara; Wunderli-Allenspach, Heidi; Beck-Sickinger, Annette G.
CORPORATE SOURCE: Institute of Biochemistry, University of Leipzig, Leipzig, D-04103, Germany
SOURCE: Journal of Medicinal Chemistry (2001), 44(9), 1341-1348
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

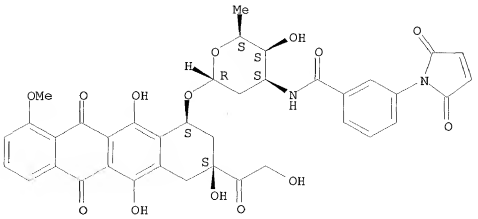
AB One of the major problems in cancer chemotherapy are the severe side effects that limit the dose of the anticancer drugs because of their unselectivity for tumor vs. normal cells. In the present work, we show that coupling of anthracyclines to peptides is a promising approach to obtain selectivity. The peptide-drug **conjugate** was designed to bind to specific receptors expressed on the tumor cells with subsequent internalization of the ligand-receptor complex. Neuropeptide Y (NPY), a 36-amino acid peptide of the pancreatic polypeptide family, was chosen as model peptide because NPY receptors are overexpressed in a no. of neuroblastoma tumors and the thereof derived cell lines. Daunorubicin and doxorubicin, two widely used antineoplastic agents in tumor therapy, were covalently **linked** to NPY via two spacers that differ in stability: an acid-sensitive hydrazone bond at the 13-keto position of daunorubicin and a stable amide bond at the 3'-amino position of daunorubicin and doxorubicin. Receptor binding of these three **conjugates** ([C15]-NPY-Dauno-HYD, [C15]-NPY-Dauno-MBS, and [C15]-NPY-Doxo-MBS) was detd. at the human neuroblastoma cell line SK-N-MC, which selectively expresses the NPY Y1 receptor subtype, and cytotoxic activity was evaluated using a XTT-based colorimetric cellular cytotoxicity assay. The different **conjugates** were able to bind to the receptor with affinities ranging from 25 to 51 nM, but only the compd. contg. the acid-sensitive bond ([C15]-NPY-Dauno-HYD) showed cytotoxic activity comparable to the free daunorubicin. This cytotoxicity is Y1 receptor-mediated as shown in blocking studies with BIBP 3226, because tumor cells that do not express NPY receptors were sensitive to free daunorubicin, but not to the peptide-drug **conjugate.** The intracellular distribution was investigated by confocal laser scanning microscopy. We found evidence that the active **conjugate** [C15]-NPY-Dauno-HYD releases daunorubicin, which is localized close to the nucleus, whereas the inactive **conjugate** [C15]-NPY-Dauno-MBS is distributed distantly from the nucleus and does not seem to release the drug within the cell.

IT **12408-02-5,** Hydrogen ion, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gradient; peptide **conjugates** for tumor-specific chemotherapy)

RN 12408-02-5 HCAPLUS
CN Hydrogen ion (8CI, 9CI) (CA INDEX NAME)

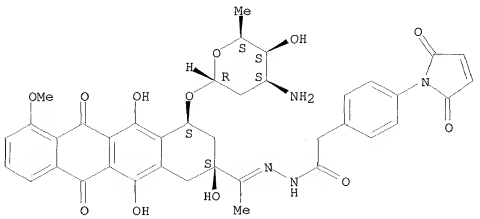
RN 188530-64-5 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)benzoyl]amino]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 342607-67-4 HCAPLUS
CN Benzeneacetic acid, 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-, [1-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]ethylidene]hydrazide (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:880603 HCAPLUS
DOCUMENT NUMBER: 134:46760
TITLE: Drug-carrier **conjugates** for drug delivery
INVENTOR(S): **Kratz, Felix**

PATENT ASSIGNEE(S): Ktb Tumorforschungsgesellschaft m.b.H., Germany
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19926475	A1	20001214	DE 1999-19926475	19990610
WO 2000076550	A2	20001221	WO 2000-EP5254	20000607
WO 2000076550	A3	20010517		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1198254	A2	20020424	EP 2000-943777	20000607

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

JP 2003501485	T2	20030114	JP 2001-502881	20000607

PRIORITY APPLN. INFO.: DE 1999-19926475 A 19990610
WO 2000-EP5254 W 20000607

AB **Conjugates** of drugs with carrier mols. are disclosed in which the carrier is a polypeptide mol. bearing one or more cysteine residue and the drug is joined to a spacer mol. that has a thiol-binding group, so that for each mole of cysteine >0.7 mol of drug is bound to the carrier by means of the thiol-binding group. An example is presented of doxorubicin **linked** to a spacer joined to a maleimide group which, in turn, can form **conjugates** with cysteine residues of human serum albumin.

IT **9001-92-7**, Proteinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(-susceptible cleavage sites; drug-carrier **conjugates** for drug delivery)

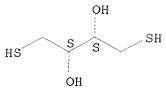
RN 9001-92-7 HCAPLUS
CN Proteinase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **59-30-3**, Folic acid, biological studies **289-95-2D**, Pyrimidine, derivs.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antagonists; drug-carrier **conjugates** for drug delivery)

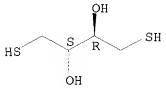
RN 59-30-3 HCAPLUS
CN L-Glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

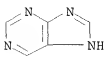


RN 6892-68-8 HCAPLUS
CN 2,3-Butanediol, 1,4-dimercapto-, (2R,3S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **120-73-0D**, 1H-Purine, derivs.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(purines, antagonists; drug-carrier **conjugates** for drug delivery)
RN 120-73-0 HCAPLUS
CN 1H-Purine (9CI) (CA INDEX NAME)



L5 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:880585 HCAPLUS
DOCUMENT NUMBER: 134:46759
TITLE: Procedure for the production of an injectable drug preparation
INVENTOR(S): **Kratz, Felix**
PATENT ASSIGNEE(S): Ktb Tumorforschungsgesellschaft m.b.H., Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19926154	A1	20001214	DE 1999-19926154	19990609
WO 2000076551	A2	20001221	WO 2000-EP5272	20000607
WO 2000076551	A3	20010816		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,

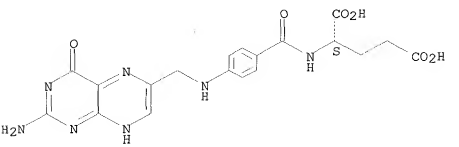
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1183050 A2 20020306 EP 2000-945721 20000607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2003501486 T2 20030114 JP 2001-502882 20000607
PRIORITY APPLN. INFO.: DE 1999-19926154 A 19990609
WO 2000-EP5272 W 20000607

AB An injectable drug form is disclosed in which the pharmacol. active agent is connected by means of a spacer mol. to a protein-binding moiety which allows the drug to bind to serum proteins such as albumins. The **linkage** between the drug and the spacer is pH-dependent or enzymically cleavable in the body, so that the active agent can be released at the target site. An example is given in which doxorubicin is **linked** to a phenylacetylhydrazone spacer which bears a maleimide group as the protein-binding moiety.

IT **59-30-3**, Folic acid, biological studies **289-95-2D**, Pyrimidine, derivs.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; procedure for the prodn. of an injectable drug prepn.)

RN 59-30-3 HCAPLUS
CN L-Glutamic acid, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]- (9CI) (CA INDEX NAME)

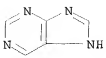
Absolute stereochemistry.



RN 289-95-2 HCAPLUS
CN Pyrimidine (8CI, 9CI) (CA INDEX NAME)

IT **312732-37-9P**
RL: BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(procedure for the prodn. of an injectable drug prepn.)

RN 312732-37-9 HCAPLUS
CN Benzeneacetic acid, 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-,



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

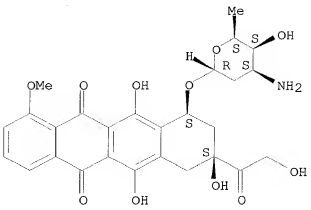
L5 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:9442 HCAPLUS
DOCUMENT NUMBER: 132:170955
TITLE: Acid-sensitive polyethylene glycol **conjugates** of doxorubicin: preparation, in vitro efficacy and intracellular distribution
AUTHOR(S): Rodrigues, Paula C. A.; Beyer, Ulrich; Schumacher, Peter; Roth, Thomas; Fiebig, Heinz H.; Unger, Clemens; Messori, Luigi; Orioli, PierLuigi; Paper, Dietrich H.; Mulhaupt, Rolf; **Kratz, Felix**
CORPORATE SOURCE: Department of Medical Oncology, Clinical Research, Tumor Biology Center, Freiburg, 79106, Germany
SOURCE: Bioorganic & Medicinal Chemistry (1999), 7(11), 2517-2524
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Coupling anticancer drugs to synthetic polymers is a promising approach of enhancing the antitumor efficacy and reducing the side-effects of these agents. Doxorubicin maleimide derivs. contg. an amide or acid-sensitive hydrazone **linker** were therefore coupled to .alpha.-methoxy-poly(ethylene glycol)-thiopropionic acid amide (MW 20000 Da), .alpha.,.omega.-bis-thiopropionic acid amide poly(ethylene glycol) (MW 20000 Da) or .alpha.-tert-butoxy-poly(ethylene glycol)-thiopropionic acid amide (MW 70000 Da) and the resulting polyethylene glycol (PEG) **conjugates** isolated through size-exclusion chromatog. The polymer drug derivs. were designed as to release doxorubicin inside the tumor cell by acid-cleavage of the hydrazone bond after uptake of the **conjugate** by endocytosis. The acid-sensitive PEG **conjugates** contg. the carboxylic hydrazone bonds exhibited in vitro activity against human BXF T24 bladder carcinoma and LXFL 529L lung cancer cells with IC70 values in the range 0.02-1.5 .mu.m (cell culture assay: propidium iodide fluorescence or colony forming assay). In contrast, PEG doxorubicin **conjugates** contg. an amide bond between the drug and the polymer showed no in vitro activity. Fluorescence microscopy studies in LXFL 529 lung cancer cells revealed that free doxorubicin accumulates in the cell nucleus whereas doxorubicin of the acid-sensitive PEG doxorubicin **conjugates** is primarily localized in the cytoplasm. Nevertheless, the acid-sensitive PEG doxorubicin **conjugates** retain their ability to bind to calf thymus DNA as shown by fluorescence and visible spectroscopy studies. Results regarding the effect of an acid-sensitive PEG **conjugate** of mol. wt. 20000 in the chorioallantoic membrane (CAM) assay indicate that this **conjugate** is significantly less embryotoxic than free doxorubicin although antiangiogenic effects were not obsd.

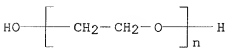
IT **23214-92-8DP**, Doxorubicin, polyethylene glycol **conjugates** of **25322-68-3DP**, Polyethylene glycol, doxorubicin **conjugates** with **258844-01-8P 258844-02-9P 258844-03-0P 258844-04-1P 258844-05-2P**

258844-06-3P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(acid-sensitive polyethylene glycol **conjugates** of doxorubicin: prepn., in vitro efficacy and intracellular distribution)
RN 23214-92-8 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

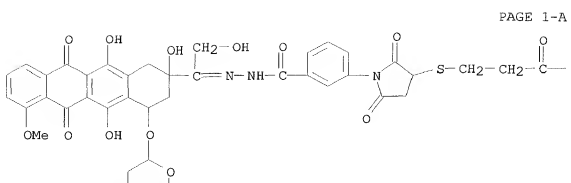


RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy- (9CI) (CA INDEX NAME)



RN 258844-01-8 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), .alpha.-[2-[[3-[[1-[3-[[2-[1-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-hydroxyethylidene]hydrazino]carbonyl]phenyl]-2,5-dioxo-3-pyrrolidinyl]thio]-1-oxopropyl]amino]ethyl]-.omega.-methoxy- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

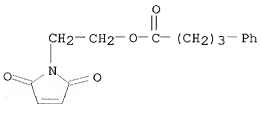
L5 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:608923 HCAPLUS
DOCUMENT NUMBER: 129:347239
TITLE: Albumin **conjugates** of the anticancer drug chlorambucil. Synthesis, characterization, and in vitro efficacy
AUTHOR(S): **Kratz, Felix**; Beyer, Ulrich; Roth, Thomas; Schuette, Mark T.; Unold, Anuschka; Fiebig, Heinz H.; Unger, Clemens
CORPORATE SOURCE: Dep. Med. Oncology, Clin. Res., Tumor Biology Center, Freiburg/Br., D-79106, Germany
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1998), 331(2), 47-53
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In efforts to improve the selectivity and toxicity profile of antitumor agents, 4 maleimide derivs. of chlorambucil were bound to thiolated human serum albumin which differ in the stability of the chem. **link** between drug and spacer. One is an aliph. maleimide ester deriv. of chlorambucil, whereas other three are acetaldehyde, acetophenone, and benzaldehyde carboxylic hydrazone derivs. HPLC stability studies at pH 5.0 with the related model compds. in which chlorambucil was substituted by 4-phenylbutyric acid, demonstrated that the carboxylic hydrazone derivs. have acid-sensitive properties. The alkylating activity of albumin-bound chlorambucil was detd. with the aid of 4-(4-nitrobenzyl)-pyridine (NBP), demonstrating that on av. 3 equiv were protein-bound. Evaluation of the cytotoxicity of free chlorambucil and the resp. albumin

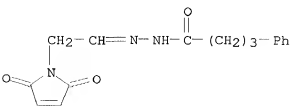
conjugates in the MCF7 mamma carcinoma and MOLT4 leukemia cell line employing a propidium iodide fluorescence assay demonstrated that the **conjugate** in which chlorambucil was bound to albumin through an ester bond was not active as chlorambucil. In contrast, the **conjugates** in which chlorambucil was bound to albumin through carboxylic hydrazone bonds were as or more active than chlorambucil in both cell lines. In particular, the **conjugate** in which chlorambucil was bound to albumin through an acetaldehyde carboxylic hydrazone bond exhibited IC50 values which were approx. 4-fold (MCF7) to 13-fold (MOLT4) lower than those of chlorambucil. Preliminary toxicity studies in mice showed that this **conjugate** can be administered at higher doses in comparison to unbound chlorambucil.

IT **215391-15-4P 215391-16-5P 215391-17-6P**
215391-18-7P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(synthesis, characterization, and in vitro efficacy of albumin **conjugates** of anticancer chlorambucil derivs.)

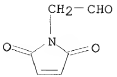
RN 215391-15-4 HCAPLUS
CN Benzenebutanoic acid, 2-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)ethyl ester (9CI) (CA INDEX NAME)



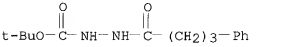
RN 215391-16-5 HCAPLUS
CN Benzenebutanoic acid, [2-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)ethylidene]hydrazide (9CI) (CA INDEX NAME)



RN 215391-17-6 HCAPLUS
CN Benzenebutanoic acid, [1-[3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)phenyl]ethylidene]hydrazide (9CI) (CA INDEX NAME)



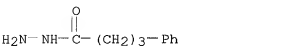
IT **215391-19-8P 215391-20-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis, characterization, and in vitro efficacy of albumin **conjugates** of anticancer chlorambucil derivs.)
RN 215391-19-8 HCAPLUS
CN Hydrazinecarboxylic acid, 2-(1-oxo-4-phenylbutyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 215391-20-1 HCAPLUS
CN Benzenebutanoic acid, hydrazide, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 39181-61-8
CMF C10 H14 N2 O



CM 2

CRN 76-05-1
CMF C2 H F3 O2

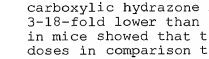
L5 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:446968 HCAPLUS
DOCUMENT NUMBER: 129:166133
TITLE: Synthesis and in Vitro Efficacy of Transferrin **Conjugates** of the Anticancer Drug Chlorambucil
AUTHOR(S): Beyer, Ulrich; Roth, Thomas; Schumacher, Peter; Maier, Gerhard; Unold, Anuschka; Frahm, August W.; Fiebig,

Heinz H.; Unger, Clemens; **Kratz, Felix**
CORPORATE SOURCE: Department of Medical Oncology, Clinical Research, Tumor Biology Center, Freiburg, 79106, Germany
SOURCE: Journal of Medicinal Chemistry (1998), 41(15), 2701-2708
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB One strategy for improving the selectivity and toxicity profile of antitumor agents is to design drug carrier systems employing sol. macromols. or carrier proteins. Thus, five maleimide derivs. of chlorambucil were bound to thiolated human serum transferrin which differ in the stability of the chem. **link** between drug and spacer. The maleimide ester derivs. were prepd. by reacting 2-hydroxyethylmaleimide or 3-maleimidophenol with the carboxyl group of chlorambucil, and the carboxylic hydrazone derivs. were obtained through reaction of 2-maleimidoacetaldehyde, 3-maleimidoacetophenone, or 3-maleimidobenzaldehyde with the carboxylic acid hydrazide deriv. of chlorambucil. The alkylating activity of transferrin-bound chlorambucil was detd. with the aid of 4-(4-nitrobenzyl)pyridine (NBP) demonstrating that on av. 3 equiv were protein-bound. Evaluation of the cytotoxicity of free chlorambucil and the resp. transferrin **conjugates** in the MCF7 mammary carcinoma and MOLT4 leukemia cell line employing a propidium iodide fluorescence assay demonstrated that the **conjugates** in which chlorambucil was bound to transferrin through non-acid-sensitive **linkers**, i.e., an ester or benzaldehyde carboxylic hydrazone bond, were not, on the whole, as active as chlorambucil. In contrast, the two **conjugates** in which chlorambucil was bound to transferrin through acid-sensitive carboxylic hydrazone bonds were as active as or more active than chlorambucil in both cell lines. Esp., the **conjugate** in which chlorambucil was bound to transferrin through an acetaldehyde carboxylic hydrazone bond exhibited IC50 values which were approx. 3-18-fold lower than those of chlorambucil. Preliminary toxicity studies in mice showed that this **conjugate** can be administered at higher doses in comparison to unbound chlorambucil. The structure-activity relationships of the transferrin **conjugates** are discussed with respect to their pH-dependent acid sensitivity, their serum stability, and their cytotoxicity.

IT **10031-93-3 56379-64-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(stability in cell-conditioned medium; synthesis and in vitro efficacy of transferrin **conjugates** of the anticancer drug chlorambucil)

RN 10031-93-3 HCAPLUS
CN Benzenebutanoic acid, ethyl ester (9CI) (CA INDEX NAME)



RN 56379-64-7 HCAPLUS
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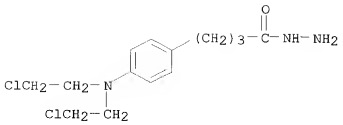

CM 2

CRN 76-05-1
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REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:186637 HCAPLUS
DOCUMENT NUMBER: 128:213389
TITLE: Antineoplastic transferrin and albumin **conjugates** of cytostatic compounds selected from anthracyclines, alkylating agents, antimetabolites, and cisplatin analogs
INVENTOR(S): **Kratz, Felix**
PATENT ASSIGNEE(S): Kratz, Felix, Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19636889	A1	19980312	DE 1996-19636889	19960911
WO 9810794	A2	19980319	WO 1997-DE2000	19970909
WO 9810794	A3	19980806		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9745489	A1	19980402	AU 1997-45489	19970909
EP 934081	A2	19990811	EP 1997-943750	19970909

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2001500133	T2	20010109	JP 1998-513144		19970909
US 6310039	B1	20011030	US 1999-254598		19990521
US 2002019343	A1	20020214	US 2001-931940		20010820
PRIORITY APPLN. INFO.:			DE 1996-19636889	A	19960911
			WO 1997-DE2000	W	19970909
			US 1999-254598	A1	19990521

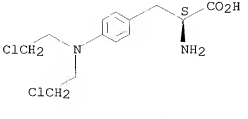
OTHER SOURCE(S): MARPAT 128:213389

AB **Conjugates** of thiolated transferrin and/or albumin with maleimide-derivatized anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), alkylating agents (chlorambucil, melphalan), antimetabolites (5-fluorouracil, 5'-deoxy-5-fluorouridine), or cisplatin analogs, where the **linkage** is through an amide, ester, imine, hydrazone, acylhydrazone, urethane, acetal, or ketal group, show high antitumor activity and are water sol. and stable under physiol. conditions, and are therefore suitable for cancer treatment. Thus, transferrin was thiolated with iminothiolane; the no. of SH groups introduced depended on the temp. and concn. ratio of iminothiolane to protein. Thiolated transferrin was **conjugated** with the 3'-amide of doxorubicin with p-maleimidophenylacetyl chloride. The product had cytostatic activity comparable to that of **unconjugated** doxorubicin against colon carcinoma HCT-116 cells in vitro.

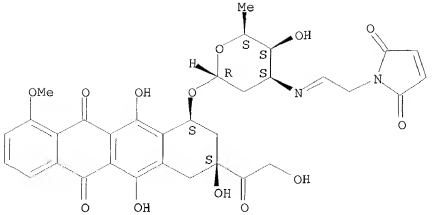
IT **148-82-3D**, Melphalan, **conjugates** with albumin and transferrin **305-03-3D**, Chlorambucil, **conjugates** with albumin and transferrin **20830-81-3D**, Daunorubicin, **conjugates** with albumin and transferrin **23214-92-8D**, Doxorubicin, **conjugates** with albumin and transferrin **35028-95-6D**, derivs., **conjugates** with albumin and transferrin **56420-45-2D**, Epirubicin, **conjugates** with albumin and transferrin **58957-92-9D**, Idarubicin, **conjugates** with albumin and transferrin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antineoplastic transferrin and albumin **conjugates** of cytostatic compds. selected from anthracyclines, alkylating agents, antimetabolites, and cisplatin analogs)

RN 148-82-3 HCAPLUS
CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)

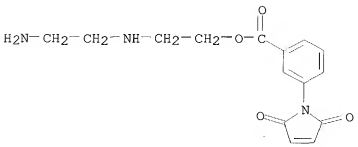
Absolute stereochemistry.



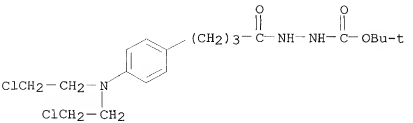
RN 305-03-3 HCAPLUS
CN Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)



RN 204200-78-2 HCAPLUS
CN Benzoic acid, 3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-, 2-[(2-aminoethyl)amino]ethyl ester (9CI) (CA INDEX NAME)



RN 204200-80-6 HCAPLUS
CN Hydrazinecarboxylic acid, 2-[4-[4-[bis(2-chloroethyl)amino]phenyl]-1-oxobutyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

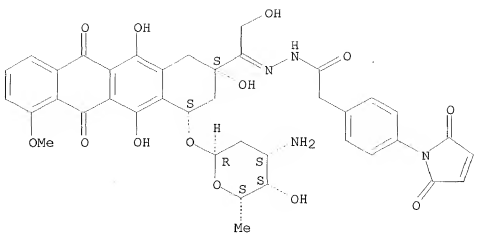
L5 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:89761 HCAPLUS
DOCUMENT NUMBER: 128:145242
TITLE: Transferrin **Conjugates** of Doxorubicin: Synthesis, Characterization, Cellular Uptake, and in Vitro Efficacy

AUTHOR(S): **Kratz, Felix**; Beyer, Ulrich; Roth, Thomas; Tarasova, Nadya; Collery, Philippe; Lechenault, Francoise; Cazabat, Annie; Schumacher, Peter; Unger, Clemens; Falken, Ulrich
CORPORATE SOURCE: Department of Medical Oncology, Clinical Research Tumor Biology Center, Freiburg, 79106, Germany
SOURCE: Journal of Pharmaceutical Sciences (1998), 87(3), 338-346
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB One strategy for improving the antitumor selectivity and toxicity profile of antitumor agents is to design drug carrier systems employing suitable carrier proteins. Thus, thiolated human serum transferrin was **conjugated** with four maleimide derivs. of doxorubicin that differed in the stability of the chem. **link** between drug and spacer. Of the maleimide derivs., 3-maleimidobenzoic or 4-maleimidophenylacetic acid was bound to the 3'-amino position of doxorubicin through a benzoyl or phenylacetyl amide bond, and 3-maleimidobenzoic acid hydrazide or 4-maleimidophenylacetic acid hydrazide was bound to the 13-keto position through a benzoyl hydrazone or phenylacetyl hydrazone bond. The acid-sensitive transferrin **conjugates** prepd. with the carboxylic hydrazone doxorubicin derivs. exhibited an inhibitory efficacy in the MDA-MB-468 breast cancer cell line and U937 leukemia cell line comparable to that of the free drug (employing the BrdU (5-bromo-2'-deoxyuridine) incorporation assay and tritiated thymidine incorporation assay, resp., IC50 .mchgt. 0.1-1 mM), whereas **conjugates** with the amide derivs. showed no activity. Furthermore, antiproliferative activity of the most active transferrin **conjugate** (i.e. the **conjugate** contg. a benzoyl hydrazone **link**) was demonstrated in the LXFL 529 lung carcinoma cell line employing a sulforhodamine B assay. In contrast to in vitro studies in tumor cells, cell culture expts. performed with human endothelial cells (HUVEC) showed that the acid-sensitive transferrin **conjugates** of doxorubicin were significantly less active than free doxorubicin (IC50 values approx. 10-40 higher by the BrdU incorporation assay), indicating the selectivity of the doxorubicin-transferrin **conjugates** for tumor cells. Fluorescence microscopy studies in the MDA-MB-468 breast cancer cell showed that free doxorubicin accumulates in the cell nucleus, whereas doxorubicin of the transferrin **conjugates** is found localized primarily in the cytoplasm. The differences in the intracellular distribution between transferrin-doxorubicin **conjugates** and doxorubicin were confirmed by laser scanning confocal microscopy in LXFL 529 cells after a 24 h incubation that revealed an uptake and mode of action other than intercalation with DNA. The relationship between stability, cellular uptake, and cytotoxicity of the **conjugates** is discussed.

IT **23214-92-8DP**, Doxorubicin, **conjugates** with transferrins
188530-64-5DP, **conjugates** with transferrins
188530-66-7DP, **conjugates** with transferrins
188530-67-8DP, **conjugates** with transferrins
202407-74-7DP, **conjugates** with transferrins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(prepn., characterization, cellular uptake, and in vitro efficacy of transferrin **conjugates** of doxorubicin)

RN 23214-92-8 HCAPLUS



L5 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:75568 HCAPLUS
DOCUMENT NUMBER: 128:212806
TITLE: Preparation, characterization and in vitro efficacy of albumin **conjugates** of doxorubicin
AUTHOR(S): **Kratz, Felix;** Beyer, Ulrich; Collery, Philippe; Lechenault, Francoise; Cazabat, Annie; Schumacher, Peter; Falken, Ulrich; Unger, Clemens
CORPORATE SOURCE: Department of Medical Oncology, Tumor Biology Center, Clinical Research, Freiburg, 79106, Germany
SOURCE: Biological & Pharmaceutical Bulletin (1998), 21(1), 56-61
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

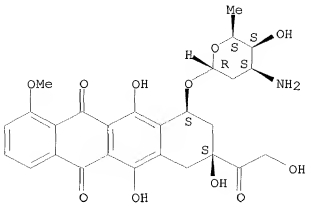
AB One strategy for improving the antitumor selectivity and toxicity profile of antitumor agents is to design drug carrier systems with suitable transport proteins. Thus, four maleimide derivs. of doxorubicin were bound to thiolated human serum albumin which differed in the stability of the chem. **link** between drug and spacer. In the maleimide derivs., 3-maleimidobenzoic or 4-maleimidophenylacetic acid was bound to the 3'-amino position of doxorubicin through a benzoyl or phenylacetyl amide bond and 3-maleimidobenzoic acid hydrazide or 4-maleimidophenylacetic acid hydrazide was bound to the 13-keto position through a benzoyl hydrazone or phenylacetyl hydrazone bond. The acid-sensitive albumin **conjugates** prepd. with the carboxylic hydrazone doxorubicin derivs. exhibited an inhibitory efficacy in the MDA-MB-468 breast cancer cell line and U937 leukemia cell line comparable with that of the free drug (using the BrdU-(5-bromo-2'-deoxyuridine)-incorporation assay and tritiated thymidine incorporation assay resp., IC50.apprx.0.1-1 .mu.M) whereas **conjugates** with the amide derivs. showed no or only marginal activity. These results demonstrate that antiproliferative activity depends on the nature of the chem. bond between doxorubicin and carrier protein. Acid-sensitive albumin **conjugates** are suitable candidates for further in vitro and in vivo assessment.

IT **23214-92-8DP,** Doxorubicin, thiolated serum albumin **conjugates** **188530-64-5DP,** thiolated serum albumin **conjugates** **188530-66-7DP,** thiolated serum albumin

conjugates 188530-67-8DP, thiolated serum albumin
conjugates 202407-74-7DP, thiolated serum albumin
conjugates
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and characterization and in vitro efficacy of albumin **conjugates** of doxorubicin against human cancer cells in relation to stability)

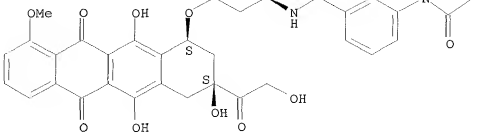
RN 23214-92-8 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 188530-64-5 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)benzoyl]amino]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 188530-66-7 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-

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FULL ESTIMATED COST                                45.33     91.11

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                -5.86    -13.02

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 10:26:00 ON 02 OCT 2003
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